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Coagulation problems in human pregnancy

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Coagulation problems in pregnancy are primarily associated with overactivity of the intrinsic clotting system. This accounts for the increased incidence of thrombo-embolism during pregnancy. Where specific obstetric complications cause clotting problems the common underlying feature is usually placental pathology as in abruptio placentae, pre-eclampsia or hydatidiform mole.

Abnormal activation of the clotting system is an early, and occasionally the first detectable feature of pre-eclampsia, but there is no evidence that this is a primary change. Therefore the role of anticoagulant treatment in the management of pre-eclampsia remains questionable. A new test for estimating factor VIII consumption is proving to be a sensitive index of early activation of the clotting system and can be used for the diagnosis of early pre-eclampsia.

Introduction

It is reasonable to suppose that the changes in the clotting system during normal human pregnancy are needed to maintain haemostasis in the utero-placental circulation before and during delivery. The increased levels of many of the clotting factors as well as the reduced activity of the fibrinolytic system would be expected to increase overall blood coagulability.

Two sorts of clinical problem arise in pregnancy which are closely linked to these changes in the clotting system – thrombo-embolism and obstetric complications which may cause abnormal intravascular coagulation (Table 1).

TABLE 1. Obstetric complications associated with abnormalities of the clotting system

Abruptio placentae	Retention of dead fetus
Amniotic fluid embolism	Septic abortion
Eclampsia/pre-eclampsia	Hypertonic saline abortion
Hydatidiform mole	

In addition, there are the separate problems presented by the specific bleeding disorders such as auto-immune thrombocytopenia or von Willebrand's disease, which are fairly rare and managed nowadays with replacement therapy if needed. Therefore these conditions will not be dealt with here.

Thrombo-embolism

The reported incidence of thrombo-embolism in pregnancy varies with the diagnostic methods used. For deep vein thrombosis the incidence ranges from 1·9/1000 if clinical criteria are used to 30/1000 (Friend and Kakkar, 1970) if more specific diagnostic investigations are used. Pulmonary embolism remains a major cause of maternal death. The risk of pulmonary embolism in pregnancy is increased in women with a history of thrombo-embolism, after prolonged antenatal stay in hospital, in older or obese patients, after Caesarean section, and where oestrogens have been used to suppress lactation (Howie, 1977).

The clinical diagnosis of thrombo-embolism is not easy. The signs of deep leg-vein thrombosis may occur where the venogram is totally normal (Nicolaides *et al.*, 1971) and, conversely, extensive thrombosis may produce no clinical signs (Flanc, Kakkar and Clarke, 1968). Massive pulmonary embolism with the sudden development of cyanosis, shock, right-sided heart strain, haemoptysis and pleuritic pain presents a clear clinical syndrome. Lesser degrees of embolism are much harder to diagnose: the most common clinical problem in pregnancy being the elucidation of isolated pleuritic pain.

The treatment of thrombo-embolism with anticoagulants is fraught with difficulties. Therefore the diagnosis should always be secured if possible by specific radiological investigation. This means venography for deep leg-vein thrombosis, and radioisotope lung-scanning for pulmonary embolus. Both investigations avoid significant radiation hazards for the fetus but can also generate their own unwanted side effects (Lea Thomas and MacDonald, 1978).

It should be remembered that thrombosis can occur elsewhere in the maternal circulation during pregnancy. Pelvic pain may indicate pelvic venous thrombosis (Kauppila, 1974); and intracranial venous sinus thrombosis is a rare but dangerous complication both antenatally and in the puerperium (Goldman, Eckerling and Gans, 1964).

The treatment of thrombo-embolism is effective anticoagulation. Heparin is preferred antenatally because it does not cross to the fetus. Continuous

intravenous heparin at 40–60 000 u./day is needed to treat established thrombo-embolism. Lower dose subcutaneous heparin at 15–30 000 u./day is appropriate for long-term prophylactic therapy. Preferably it should be monitored by regular estimation of blood heparin levels which should be titrated to about 0·5 u./ml.

Oral anticoagulants cross the placenta. Warfarin seems to have 2 distinct injurious effects on the fetus. The first is a teratogenic effect associated with first trimester ingestion causing hypoplasia of nasal structures and radiologically stippled epiphyses. The second is possibly a haemorrhagic effect adversely affecting central nervous system development during the second and third trimester (Hall, 1976). For these reasons, warfarin should not be used unless the indications override the possibility of fetal damage.

Clotting abnormalities and specific obstetric complications

The problems listed in Table 1 share only one common factor, namely some degree of placental pathology. The abnormal intravascular coagulation which is typical in these situations can develop suddenly or can evolve slowly over weeks or months.

Abruptio placentae and amniotic fluid embolism

These catastrophes cause massive, acute activation of the clotting system, secondary depletion of coagulation factors leading rapidly to coagulation failure. Abruptio placentae occurs commony enough for the problems to be familiar to practising obstetricians. The more extensive the placental separation the greater the clotting failure caused by depletion of not only fibrinogen, but factors II (prothrombin) V, VIII as well as of circulatory platelets. The fibrin that is produced is partially lysed to fibrin/fibrinogen degradation products (FDP) whose circulatory levels are massively increased.

The management of abruptio placentae requires prompt correction of circulatory collapse from blood loss, using fresh blood and fresh frozen plasma. The uterus then needs to be emptied, either vaginally, or by Caesarean section if the abruption is both small and of recent onset so that the fetus survives and the clotting problems have not had time to develop fully.

Abruptio placentae may occur in the context of established pre-eclampsia, or alternatively in apparently healthy women without any warning. In the latter cases it is possible that undetected clotting abnormalities may have preceded or even predisposed to the placental separation. For example, it is possible that placental infarcts may predispose to placental abruption. These may be clinically silent but cause clotting abnormalities such as increased factor VIII consumption (see below).

Recently a patient has been described with recurrent placental abruptions in whom investigations suggested abnormally increased fibrinolytic activity. This was treated with apparent success with the fibrinolysis inhibitor tranexamic acid (Astedt and Nilsson, 1978).

Amniotic fluid embolism is at once rarer and more lethal – the maternal mortality is more than 80%. Amniotic fluid enters the maternal venous circulation, by an unknown mechanism, usually at or just before delivery. Although coagulation failure occurs rapidly the clinical presentation is predominantly of an almost complete shut-down of the pulmonary circulation, comparable to the 'shock-lung' syndrome. Thus the signs are of sudden extreme shock with cyanosis, followed by the onset of intractable uterine bleeding. The coagulation abnormalities are ascribed to the thromboplastic activity of amniotic fluid: experimentally they can be mimicked by venous infusion of amniotic fluid from a normal term pregnancy (Yaffe *et al.*, 1977).

Pre-eclampsia and hydatidiform mole

Not only is hydatidiform mole a cause of early atypical pre-eclampsia but it causes coagulation abnormalities which are very similar to those of pre-eclampsia (Tsakok, Koh and Ratnam, 1976). There is general agreement that in pre-eclampsia the clotting system is abnormally activated but it is still disputed that these changes are an invariable feature of the disorder (Pritchard, Cunningham and Mason, 1976). Many different clotting abnormalities have been noted (Table 2). In the fulminating stages of pre-eclampsia these evolve into a frank disseminated intravascular coagulation which causes widespread fibrin deposition in the microcirculation. This in

TABLE 2. Clotting changes in pre-eclampsia

1. Raised serum fibrin/fibrinogen degradation products
   Bonnar, McNicol and Douglas, 1971
   Henderson, Pugsley and Thomas, 1970
   Gordon *et al.*, 1976
2. Raised serum soluble fibrinogen-fibrin complexes
   McKillop *et al.*, 1977
3. Thrombocytopenia
   Howie *et al.*, 1976
   Trudinger, 1976
   Bonnar *et al.*, 1971
4. Reduced platelet aggregation with collagen
   Reduced platelet 5-hydroxy-tryptamine content
   Whigham *et al.*, 1978
5. Increased platelet size
   Bolton, Redman and Stirrat, 1978
6. Impaired fibrinolysis
   Bonnar *et al.*, 1971
7. Increased factor VIII consumption
   Redman *et al.*, 1977

turn is responsible for some of the late features of pre-eclampsia including abnormal pulmonary circulation (Birmingham Eclampsia Study Group, 1971) and micro-angiopathic haemolytic anaemia (Brain, Kuah and Dixon, 1967). This complication can cause a very sudden and unexpected fall in the haemoglobin (Table 3). The presentation in these circumstances may be confused with thrombotic thrombocytopenic purpura (Schwartz and Brenner, 1978). The post-mortem appearances are consistent with the clinical picture with evidence of widespread fibrin deposition in the small vessels (McKay *et al.*, 1953).

TABLE 3. Acute micro-angiopathic haemolysis occurring in a primigravida with severe pre-eclampsia

Date	Hb (g/dl)	Reticulocyte count	
25.1.71	11·9	—	
28.1.71	12·9	0·6%	
29.1.71	10·7*	2·0%	
			Delivery
3.2.71	6·8*	4·6%	
6.2.71	7·2*	13·3%	
19.2.71	10·5	4·2%	

* RBC fragmentation.

There is evidence that the clotting problems may contribute to the glomerular pathology of pre-eclampsia. Biopsy studies show a characteristic swelling of the glomerular endothelial cells, within the cytoplasm of which, fibrin can be demonstrated by immunofluorescence (Morris *et al.*, 1964). The lesions are not specific but occur also after abruptio placentae and in the haemolytic uraemic syndrome (Thomson *et al.*, 1972) both of which share the coagulation abnormalities of pre-eclampsia.

Preceding the fulminating stages of pre-eclampsia, disseminated intravascular coagulation is not present. Therefore the serum FDPs are normal and many of the components of the clotting system are normal for the maturity of the pregnancy. In a thorough serial study, Condie (1976) could not identify early changes in many different specific clotting tests in the 12 of 60 primigravidae who developed pre-eclampsia. This seemed to confirm an earlier report involving serial measurements of serum and urine FDPs (Naish *et al.*, 1973).

Nevertheless it has been shown that coincidental with but not earlier than the onset of early pre-eclampsia the platelet count begins to fall implying but not proving the onset of increased platelet consumption (Redman, Bonnar and Beilin, 1978).

The most definitive demonstration of early coagulation abnormalities in pre-eclampsia has depended on the introduction of a sensitive test for demonstrating factor VIII consumption (Denson, 1977). This depends on the simultaneous measurement of the haemophilia factor – factor VIII clotting activity (VIII CA) and factor VIII related antigen (VIII RA) which is thought to be the same as the von Willebrand factor. If the levels of these 2 factors are expressed as a percentage of average normal then the mean difference between the 2 is by definition zero in normal subjects. Stress, exercise and catecholamine infusions increase both factors in parallel so that there is no disparity in their circulating levels (Denson, 1973). When estimated by the 2-stage assay VIII CA is destroyed by thrombin (Denson, 1977) whereas VIII RA is not. When the clotting system is activated, the circulating levels of both factors increase rapidly as a secondary response, but because VIII CA is being destroyed by thrombin its final level is lower than that of VIII RA and the difference between the 2 levels is a reflection of the extent of factor VIII consumption.

Using this test it can be shown that normal pregnancy is associated with increased factor VIII consumption which is further exaggerated when preeclampsia develops (Denson, 1977; Redman *et al.*, 1977; Thornton and Bonnar, 1977). In pre-eclamptic women increased factor VIII consumption correlates particularly with the degree of the hyperuricaemia which is also characteristic of severe pre-eclampsia (Redman *et al.*, 1976).

Abnormally high factor VIII consumption was not consistently the first detectable change of pre-eclampsia in a serial study (Redman *et al.*, 1977). However, in 19 of 30 women who developed pre-eclampsia there was a tendency for the clotting changes to coincide with or precede the other signs of pre-eclampsia.

This series included 2 patients of particular interest. The first was a chronically hypertensive woman who presented a 17 weeks' gestation in her third pregnancy having had 2 previous stillbirths associated with pre-eclampsia. At presentation, factor VIII consumption was already abnormal and could not be corrected by a combination of low-dose subcutaneous heparin and oral dipyridamole. At 22 weeks' gestation, overt pre-eclampsia developed which progressed to an intrauterine death at 28 weeks. At no stage did she have proteinuria.

The second patient, a primigravida, developed abnormal factor VIII consumption and hyperuricaemia, both typical of pre-eclampsia. Her blood pressure always remained at normal levels and she did not develop proteinuria. At 38 weeks she delivered a live female infant weighing 2·8 kg. Since this pregnancy was reported, the same patient has been serially studied in her second pregnancy during which her factor VIII consumption remained

normal. She thus demonstrated many of the features of pre-eclampsia except for hypertension, suggesting the possibility that pre-eclampsia may have closely related normotensive variants (Redman *et al.*, 1977).

Clotting tests for the diagnosis of pre-eclampsia

It has been suggested that tests of clotting function alone can be used to measure the severity of pre-eclampsia (Howie *et al.*, 1976). However, the proposed 'coagulation index' proved not to be discriminating when applied prospectively (Dunlop *et al.*, 1978). The latter conclusion is not surprising because the component tests of the 'coagulation index' are all relatively insensitive, and the syndrome of pre-eclampsia is not consistent enough to allow reduction to this sort of stereotype. Although increased factor VIII consumption is usually an early feature of the disorder it occasionally is not. On the other hand investigators in the U.K. are agreed that late severe pre-eclampsia is always accompanied by detectable clotting abnormalities. In these circumstances, the diagnosis is clinically obvious and laboratory tests of clotting function are not diagnostically useful. In contrast, when pregnancy is complicated by mild hypertension of uncertain aetiology, the demonstration of abnormal activation of the clotting system establishes the diagnosis of pre-eclampsia, as other forms of mild hypertension do not cause these changes (Howie *et al.*, 1976). The best test in these circumstances is undoubtedly the measurement of factor VIII consumption (Redman *et al.*, 1977).

Although falls in the platelet count are an early feature of pre-eclampsia these changes only become detectable by studying a large number of patients and averaging the results. Individual counts, because of the variability between measurements and between patients, are not diagnostically useful.

These studies have not resolved the basic questions concerning the role of the clotting system in the pathogenesis of pre-eclampsia. It is clear that the clotting activation is detectable early enough for it not to be a secondary effect of the hypertension of eclampsia, but not so early as clearly to implicate the changes as primary. It is also clear that the clotting activation can be extraordinarily resistant to anticoagulant therapy.

Anticoagulant treatment of pre-eclampsia

The use of heparin or other anticoagulants in established pre-eclampsia is hazardous and unjustified because it seems neither to improve nor retard the progression of the disorder (Howie, Prentice and Forbes, 1975). Prophylactic anticoagulation has been described in isolated uncontrolled reports (Valentine and Baker, 1977) with apparent but not uniform success. A controlled trial of such treatment is needed but would only be possible on a multicentre basis as there are only very few women for whom such drastic measures are appropriate.

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